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Gray and white matter imaging: a biomarker for cognitive impairment in early Parkinson's disease?

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ABSTRACT

Background

To investigate the cortical and white matter changes which underlie cognitive impairment in patients with incident Parkinson disease (PD) disease using voxel-based morphometry and diffusion tensor imaging (DTI).

Methods

Newly diagnosed non-demented PD (n=125) and control subjects (n=50) were recruited from the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's disease study and completed cognitive assessments and 3T structural and diffusion tensor MR imaging. Voxel-based morphometry was performed to investigate the relationship between gray matter volume and cognitive ability. Microstructural white matter changes were assessed with DTI measures of fractional anisotropy (FA) and mean diffusivity (MD) using tract-based spatial statistics.

Results

Increased MD was seen bilaterally in subjects with PD relative to controls (*P*=0.019). Increased MD was associated with performance on the semantic fluency and Tower of London tasks in frontal and parietal white matter tracts including the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus. There was no difference in total gray matter volume between the groups, however, bilateral reductions in frontal and parietal gray matter volume were associated with reduced performance on measures of executive function in the PD subjects.

Conclusions

At the earliest stages of PD, regionally specific increases in central white matter MD are present and suggest early axonal damage. Such changes are not accompanied by significant gray matter volume

loss and are consistent with proposed models of the pathological progression of the disease. Structural MRI, especially DTI analysis, offers potential as a non-invasive biomarker reflecting cognitive impairment in PD.

INTRODUCTION

The early identification of Parkinson's disease (PD) patients at high risk of developing Parkinson's disease dementia (PDD) is of prognostic importance. Additionally, it enables clinical trials of disease modifying interventions targeted at dementia to be instituted early in the disease process prior to extensive neuronal loss. Mild cognitive impairments occur in 20 – 40% of patients with newly diagnosed PD[1-4]; these patients may be at highest risk of subsequently developing PDD.[5] This process is driven by disruption of dopaminergic, cholinergic and serotonergic neurotransmitter systems secondary to abnormal α-synuclein aggregation; however, cortical Lewy body disease and the contribution of amyloid, tau and vascular pathologies can also be factors.[6, 7]

Structural MRI is an established biomarker in observational and interventional studies of Alzheimer's disease. Most studies using region of interest (ROI), voxel-based morphometry (VBM) and cortical thickness analysis approaches have not found significant gray matter loss in patients with early, cognitively intact PD (PD-NC), although mild posterior atrophy was reported in one series. [8-12] Gray matter loss involving parietal, temporal, and occipital regions is a consistent finding in PDD.[8, 11, 13-18] More limited gray matter loss has been reported in subjects with PD-MCI.[8, 11, 17, 19, 20] In a two year longitudinal study, PD-MCI subjects who developed dementia had lower gray matter density at baseline in the prefrontal cortex, insular cortex, and caudate nuclei than PD-MCI patients who did not subsequently convert.[21]

Diffusion tensor imaging (DTI) is a sensitive technique for detecting microstructural white matter pathology. Through quantifying the magnitude and directionality of the motion of water molecules it provides an *in vivo* surrogate measure of the integrity of tissue microstructure. Degeneration of structural barriers such as myelin and cell membranes increases mean diffusivity (MD) and lowers the directionality of its flow, measured as fractional anisotropy (FA). Tract-based spatial statistics (TBSS) interrogates the integrity of white matter tracts without the limits of the operator-dependent ROI approach.[22] Changes in FA and MD have been reported in both PDD[12, 23, 24] and PD-MCI.[23]

We sought evidence of alterations in regional gray matter volume and integrity of the principal white matter tracts in patients with newly diagnosed PD. We hypothesized that because increased MD is a sensitive marker of white matter damage, changes in MD would be detectable prior to reduced FA[23, 25] and significant gray matter loss.

METHODS

Subjects

All patients and controls were enrolled prospectively as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's Disease (ICICLE-PD) Study.[4, 26] All patients with newly diagnosed PD attending movement disorder, neurology, and geriatric medicine clinics in Newcastle and Gateshead between 1st June 2009 and 31st December 2011 were invited to participate. Enrolled subjects fulfilled the UK Brain Bank Criteria for idiopathic PD.[27] Healthy and unrelated control subjects were recruited from the local community.

Exclusion criteria comprised: patients with parkinsonism diagnosed prior to the onset of the study; insufficient working knowledge of English; significant cognitive impairment or dementia at presentation; and the use of antipsychotic medication. Patients were reviewed after 18 months to ensure that other causes of parkinsonism were excluded.

The study was approved by the Newcastle and North Tyneside Research Ethics Committee. All subjects provided written informed consent.

Clinical and neuropsychological assessment

Clinical, neuropsychological, and imaging assessments were completed for each participant within a 4 month period. Assessments included a standardized neurological examination, Hoehn and Yahr (H&Y) staging,[28] the Movement Disorders Society-revised Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III,[29] and the Geriatric Depression Scale (GDS-15).[30] Patients were assessed while

taking their normal regimen of dopaminergic and other medications. Dopaminergic medication doses were standardized and are presented as levodopa equivalent daily dose (LEDD).[31]

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE)[32] and Montreal Cognitive Assessment (MoCA).[33] Attention was measured using tests from the Cognitive Drug Research (CDR) battery. Scores of simple reaction time, choice reaction time, and digit vigilance were summed to produce a composite power of attention (PoA) score.[34] Memory was assessed with the spatial recognition memory, pattern recognition memory, and paired associates learning subsets from the Cambridge Neuropsychological Test Automated Battery (CANTAB).[35] Executive function was measured using tests of phonemic fluency (words beginning with F, A, and S for 60 seconds each)[36] and semantic fluency (animals named in 90 seconds)[37] and with the Tower Of London task from the CANTAB battery.[38]

MRI acquisition

All images were acquired using a 3T Intera Achieva scanner (Philips Medical Systems, Eindhoven, Netherlands) with an 8-channel receiver head coil in a single session. A standard sagittal T1-weighted volumetric scan was acquired covering the whole brain using a magnetization prepared rapid gradient echo (MP-RAGE) sequence: echo time (TE) = 4.6ms; repetition time (TR) = 9.6ms; flip angle=8°, SENSE factor = 2. In-plane field of view (FOV) = 240x240mm, slice thickness = 1.2mm, voxel size = 1.15×1.15mm. DTI acquisitions were based on a 2-dimensional diffusion-weighted, spin-echo, echo planar imaging sequence with 59 slices: TR=6100ms; TE=70ms; flip angle=90°; voxel size= 2.1x2.1mm; slice thickness = 2.1mm; FOV=270x270mm. Diffusion-weighting was performed in 64 uniformly distributed directions (diffusion b=1000 $s.mm^{-2}$) and in 6 acquisitions without diffusion weighting (b= 0 $s.mm^{-2}$).

MRI pre-processing

Images were inspected for any artefacts or gross abnormalities and were processed using Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and MATLAB 7.14 (Math-Works, Natick, MA, USA).[39] T1-weighted images were segmented into gray matter, white matter, and cerebral spinal fluid (CSF) using the standard unified segmentation sequence in SPM8. These images were also inspected for segmentation classification errors. A study-specific gray matter template was created from all patients and controls using the diffeomorphic anatomical registration through exponentiated Lie algebra (DARTEL) toolbox in SPM8.[40] Gray matter data were spatially normalized and warped in DARTEL and transformed to Montreal Neurological Institute (MNI) space (http://www.mni.mcgill.ca). Images were Jacobian modulated to preserve the relative volumes of gray matter following normalization. An 8mm full-width half maximum (FWHM) Gaussian kernel was used to smooth the images. The smoothed, modulated and normalized gray matter datasets were used for the statistical analyses. Total intracranial volume (TIV) was calculated by summing the total tissue assignments to gray matter, white matter, and CSF from probability maps generated in the initial segmentation step.

DTI pre-processing

Pre-processing was performed using TBSS in FSL (http://fsl.fmrib.ox.ac.uk/fsl/tbss).[22] To correct for distorting effects of eddy currents a modified version of the technique described by Shen *et al*[41] was used with an affine registration to register pairs of diffusion-weighted images together. The diffusion-weighted images were then co-aligned with a rigid body registration to the b = 0 $s.mm^{-2}$ image. MD and FA maps were calculated using the FSL tensor analysis of the aligned diffusion-weighted images at each brain voxel. First, the individual FA images from all subjects were each nonlinearly aligned to the pre-defined FSL FMRIB58 FA map using a resolution of 1mm in the standard MNI152 space. The data were checked visually to ensure accuracy of the nonlinear transformation process. A mean FA image was created and thinned to create a mean FA skeleton, which represented the centers of all tracts common to the group. Finally, the aligned FA and MD

image for each subject was projected onto the constructed skeleton. Voxel-wise statistical analyses of FA and MD data were performed using TBSS to compare group differences between the white matter skeletons.

Statistical analyses

Clinical and neuropsychological data were analyzed with Statistical Package for Social Sciences (SPSS version 19). Independent *t*-tests were used to compare normally distributed continuous variables and the Mann-Whitney U test was used for continuous data without a normal distribution. Pearson Chi squared tests were used to compare categorical data, except where the number in a category was less than five, in which case Fisher's exact test was used. Significant results were reported at a $P<0.05$. Bonferroni adjustment was performed to correct for multiple testing of neuropsychological data, yielding a $p < 0.007$ level of significance. Consistent with recent recommendations,[42] and to make this study comparable with the work of others,[43, 44] a test score was considered impaired if it was 1.5 standard deviations (SD) below the mean score of the control subjects.

Gray matter volume differences were assessed using one way ANOVAs in the SPM8 General Linear Model based on random Gaussian field theory. An absolute threshold mask of 0.1 was used in all gray matter analyses. Age, TIV, and education were included as covariates in all multiple regression analyses. MDS-UPDRS part III score was included as a covariate for the PD subjects. The relationship between gray matter volumes and cognitive test performance was examined. Mean regional grey matter volume differences between groups (Control *vs*. PD-NC, PD-NC *vs.* $PD_{\text{-impaired-test}}$, Control *vs.* $PD_{\text{-impaired–test}}$) were compared by ANCOVA in SPM8, impaired being defined as test performance below 1.5 SD the normative mean. Reverse contrasts were performed for all analyses. Significant clusters were identified using a voxel-wise uncorrected threshold of $p<0.001$. Clusters were regarded as significant if their extent exceeded 100 voxels. To control for multiple comparisons a family-wise error (FWE) threshold of $p_{FWE\text{-}corr}<0.05$ was applied. The anatomical location was determined using the Talairach daemon (http://talairach.org/).

Differences in MD and FA were compared between groups (Control *vs.* PD-NC, PD-NC *vs*. $PD_{\text{-impaired-test}}$, Control *vs.* $PD_{\text{-impaired–test}}$) with a permutation-based, non-parametric test, 2-sample, unpaired t-test in the FSL "randomize" program. Age and education were included as covariates. Separate FA and MD models excluding the controls assessed the PD subjects (PD-NC and $PD_{\text{-impaired-test}}$) with the same covariates plus MDS-UPDRS III score. For each contrast, 5000 permutations of the data were generated producing statistical maps uncorrected and FWE-corrected for multiple comparisons. Statistical maps were interrogated using a corrected threshold of $P<0.05$. The threshold-free cluster enhancement (TFCE) algorithm was used to identify significant clusters and control for multiple comparisons.[45] Regions showing significant differences between groups were located and labelled by mapping the statistical map to the John Hopkins University DTI white matter atlas within FSL.

RESULTS

Participant characteristics

Table 1 shows that subject groups were similar in age, gender, and education. Although those with PD reported more depressive symptoms on the GDS-15 compared with controls, there was no difference in the prevalence of clinically diagnosed depression. Nor were there significant differences in the prevalence of cardiovascular disease risk factors.

Table 1. Demographic and clinical characteristics of the Parkinson's disease and control subjects.

The results of the cognitive testing are shown in Table 2. After Bonferroni correction for multiple testing, subjects with PD had small, but significant, reductions in performance on tests of global cognition and all domain specific cognitive tests compared with controls.

Table 2. Cognitive test data of the Parkinson's disease and control subjects.

Voxel-based morphometry

There was no significant difference in total or regional gray matter volumes between the entire PD group and the control subjects (P=0.58), nor following correction for total intracranial volume (P=0.42). Reduced gray matter volume in frontal, parietal, and temporal areas in the PD subjects was associated with poorer performance on the semantic fluency task ($P_{FWE\text{-}corr}$<0.05) (Table 3 and Figure 1a). Reduced gray matter volume in frontal and parietal areas was evident in PD subjects with impaired semantic fluency ($PD_{\text{-impaired-SF}}$), when compared with PD subjects with normal fluency performance and the control subjects. A relationship between reduced gray matter volumes in frontal and parietal areas and poor performance on the executive Tower of London task was also observed in PD subjects (Figure 1b). However, no mean differences were seen between groups (Control *vs*. PD-NC, PD-NC *vs*. $PD_{\text{-impaired-ToL}}$ or Control *vs.* $PD_{\text{-impaired-ToL}}$). There was no significant association between gray matter volume and performance on any of the other cognitive tests.

Figure 1. Anatomical location of clusters of reduced grey matter volume associated with cognitive task performance.

Table 3. Anatomical location of clusters of reduced gray matter volume associated with cognitive task performance.

Diffusion tensor imaging

Averaged across the entire white matter, PD subjects had greater MD than controls (0.758 x $10^{-3}mm^2/s$, range 0.717 – 0.957 *vs*. 0.752 x $10^{-3}mm^2/s$, range 0.701 – 0.893, P=0.019). Interrogation with TBSS showed MD increases bilaterally in frontal and parietal subcortical tracts including the forceps minor, cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, corpus callosum, and internal capsule (Figure 2A and 2B). These changes were also observed in PD subjects with impaired semantic fluency ($PD_{\text{-impaired-SF}}$) relative to PD-NC and controls (Figure 2C). There were no areas where the controls had higher MD values than the subjects with PD. There was no difference in total FA between the control and PD

subject groups (0.42, range 0.37 – 0.48 *vs*. 0.42, range 0.32 – 0.48, *P*=0.255), nor was there any significant association between FA and cognitive test performance.

Figure 2. Associations between MD and performance on the semantic fluency and Tower of London tasks.

DISCUSSION

In this large series of patients with newly diagnosed PD we found that altered MRI measures of white matter integrity and gray matter volume correlated with cognitive decline. The principal findings were: (1) Increases in the MD of central white matter tracts were detectable in the absence of reductions in either FA or gray matter volume; (2) Increased MD in frontal and parietal tracts and reduced gray matter volume in frontal, parietal, and temporal areas correlated with poor performance on the semantic fluency and executive Tower of London tasks.

These findings in our cohort of patients with newly diagnosed PD, extend the work of Melzer *et al* [23] who observed increased MD in the absence of significant reductions in FA in patients with established PD targeting frontal and parietal tracts with involvement of the external capsule, corticospinal tract, corpus callosum, inferior occipital fasciculus, and inferior longitudinal fasciculus. Together, these results indicate that degeneration of central white matter tracts occurs early in PD and may underlie early cognitive dysfunction. Widespread increases in MD involving the major white matter tracts have been reported in PDD.[23] TBSS has detected reductions in FA in the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, and cingulum in PDD relative to age-matched controls.[12] In the same study, patients with PDD had lower FA values in the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, cingulum, and corpus callosum compared with PD-NC subjects. However, these changes were not present in PD-NC subjects, supporting our findings and suggesting that decreases in FA appear later than rises in MD during the disease.

Increases in MD may occur with minimal or even absent alterations in FA and have been observed in studies of both AD and PD.[23, 25] Although the pathological substrate underlying DTI changes is unclear, such changes may result from similar proportional variations in the measured tensor dimensions within the diffusion ellipsoid caused by the neurodegenerative process[25] and not solely changes in the longitudinal diffusivities. The pathogenesis of white matter damage in PD is not well understood. Lewy neurites are the axonal manifestation of α-synuclein pathology and may be associated with impaired axonal transport with subsequent microstructural changes in the axon or surrounding myelin. Indeed, there is now evidence to suggest that PD is primarily a result of synaptic dysfunction with early axonal transport problems leading to subsequent cell death.[46]

Our finding of normal cortical volumes in newly diagnosed PD-NC patients is in line with other VBM studies of early PD [10, 11] and Braak neuropathological staging of the disease. [47] We are aware of only one other study of PD-NC patients, and this reported a small cluster of gray matter loss in the occipital lobe relative to controls.[8] In PD-MCI, gray matter loss is evident in temporal, parietal, and frontal regions.[11, 19, 21] Subsequently, with disease progression and the onset of dementia, diffuse gray matter loss becomes evident.[11, 13]

The association of raised MD and reduced frontal gray matter volume changes with impaired semantic fluency in early PD is a novel finding. In established PD, gray matter density changes in the inferior and middle frontal gyrus and in the temporal lobe have been reported to correlate with semantic fluency performance.[48] Semantic fluency is more than a measure of executive function and is closely related to temporal lobe function. In PD it is reported to be more significantly impaired relative to phonemic fluency.[49] This may indicate that the cognitive speed and retrieval of semantic items may represent an additional dysfunction of semantic memory.[49] Longitudinal studies of cognition in PD report that impaired semantic fluency may herald the development, or be an early feature, of PDD.[50, 51]

The involvement of the cingulate gyrus and its white matter connections to the thalamus and entorhinal cortex via the cingulum in PD is noteworthy. The cingulate is critical to the regulation of mood and autonomic function; moreover, it plays a key role in working and planning memory, attention and visuospatial skills, all of which may be impaired in early PD. It is reported to be particularly vulnerable to Lewy pathology and may be one of the earliest sites of limbic involvement in PD MRI studies report cingulate grey matter loss in PDD and changes in this structure detectable with MRI may prove a useful marker of early disease progression.[11, 15]

Strengths of our study include a large and well characterized incident cohort of patients with early PD. All subjects were imaged using the same 3T scanner. The inclusion of a control group, well matched for age, gender, and level of education permitted the generation of appropriate normative cognitive reference data. We employed validated clinical and cognitive assessments which have previously been adopted by observational and interventional studies of PD and cognition. Because the prognostic implications and neuroanatomical mechanisms of cognitive decline in PD are poorly described we avoided a generic "PD-MCI" classification and examined performance on each cognitive test separately. In doing so we hoped to gain a better appreciation of the neuroanatomical correlates and temporal progression of changes associated with cognitive decline in PD.

Our large cohort permitted the generation of study specific templates/skeletons for the imaging analyses, without reliance upon the standard templates included within analysis software packages which are generated from younger subjects. The advantage of using TBSS for analyzing diffusion data is that it combines the ability to interrogate all white matter without the limitations of an *a priori* ROI approach. Through enhanced alignment of the central white matter during the registration and skeletonisation steps, the use of non-parametric statistics and the specific TFCE method, TBSS has been shown to be more sensitive than voxel-based approaches. However TBSS is biased towards the central white matter tracts and less sensitive to changes in peripheral white

matter tracts, therefore we may have been able to detect fewer MD and FA changes in these regions.[52]

Our adoption of the UK Brain Bank criteria and use of a longitudinal study design should have minimized possible misdiagnoses.[26, 27] Only a small proportion of patients were drug naïve, however, as reflects current clinical practice, MDS guidance, and other published work.[8, 11, 21, 23, 42]

By performing analysis of cortical gray matter volumes and measuring the integrity of the underlying white matter, we have shown that MRI has the potential to become a biomarker that is associated with cognitive function in PD. Our results suggest increased diffusivity is detectable before changes in gray matter volume. Future work will be aimed at establishing the temporal nature of gray and white matter abnormalities in PD and how these and the baseline changes correlate with subsequent cognitive decline.

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AUTHOR ROLES

Dr Duncan was involved with the conception, organization, and execution of the study. He was also involved with participant recruitment, clinical assessment, data collection, and statistical analysis. He drafted the manuscript.

Dr Firbank was involved with MRI data analysis and reviewed the manuscript.

Dr Yarnall was involved with participant recruitment, clinical assessment, data collection, and data analysis. She reviewed the manuscript.

Dr Khoo was involved with the study design and coordination of the study. He was also involved with participant recruitment, clinical assessment, and data collection. He reviewed the manuscript.

Professor Brooks was a principal investigator and co-applicant for the funding grant. He was involved in the study supervision and reviewed the manuscript.

Professor Barker was a principal investigator and co-applicant for the main funding grant. He was involved with the study design and reviewed the manuscript.

Professor Burn was the chief investigator and main applicant for the funding grant. He was involved with the study design, supervised the study, and reviewed the manuscript.

Professor O'Brien was a principal investigator and co-applicant for the funding grant. He was involved in the study supervision, reviewed, and approved the final manuscript.

CONFLICT OF INTEREST

None

FINANCIAL DISCLOSURES

Dr Duncan was supported by a grant from the Newcastle University Lockhart Parkinson's Disease Research Fund. He has received educational grants from UCB, Teva-Lundbeck, Genus, and Abbvie for attending educational events.

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Professor Brooks has received grants from the EU, MRC (UK), Michael J Fox Foundation, Parkinson's UK, Alzheimer's Research Trust, Danish Council for Independent Research, the Lundbeck Foundation, and GE Healthcare. He is a consultant to GE Healthcare, Cytox, Acadia, and Shire Pharmaceuticals. He has received honoraria from GSK, UCB, Pharmacia, Janssen, Astra Zeneca, and Novartis.

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REFERENCES

1. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005;65:1239-1245.
2. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G, Norwegian ParkWest Study G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009;72:1121-1126.
3. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127:550-560.
4. Yarnall AJ, Breen DP, Duncan GW, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology 2014;82:308-316.
5. Broeders M, de Bie RM, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology 2013;81:346-352.
6. Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64:1404-1410.
7. Compta Y, Parkkinen L, O'Sullivan SS, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011;134:1493-1505.
8. Song SK, Lee JE, Park HJ, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. Mov Disord 2011;26:289-296.
9. Agosta F, Canu E, Stojkovic T, et al. The topography of brain damage at different stages of Parkinson's disease. Hum Brain Mapp 2013;34:2798-2807.
10. Dalaker TO, Zivadinov R, Larsen JP, et al. Gray matter correlations of cognition in incident Parkinson's disease. Mov Disord 2010;25:629-633.
11. Melzer TR, Watts R, MacAskill MR, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2012;83:188-194.
12. Hattori T, Orimo S, Aoki S, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 2012;33:727-739.
13. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127:791-800.
14. Junque C, Ramirez-Ruiz B, Tolosa E, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. Mov Disord 2005;20:540-544.
15. Nagano-Saito A, Washimi Y, Arahata Y, et al. Cerebral atrophy and its relation to cognitive impairment in Parkinson's disease. Neurology 2005;64:224-229.
16. Weintraub D, Doshi J, Koka D, et al. Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol 2011;68:1562-1568.
17. Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007;78:254-259.
18. Pereira JB, Ibarretxe-Bilbao N, Marti MJ, et al. Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding, and cortical thickness. Hum Brain Mapp 2012;33:2521-2534.
19. Mak E, Zhou J, Tan LC, Au WL, Sitoh YY, Kandiah N. Cognitive deficits in mild Parkinson's disease are associated with distinct areas of grey matter atrophy. J Neurol Neurosurg Psychiatry 2014;85:576-580.
20. Pagonabarraga J, Corcuera-Solano I, Vives-Gilabert Y, et al. Pattern of regional cortical thinning associated with cognitive deterioration in Parkinson's disease. PLoS One 2013;8:e54980.
21. Lee JE, Cho KH, Song SK, et al. Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 2014;85:7-16.

22. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31:1487-1505.
23. Melzer TR, Watts R, MacAskill MR, et al. White matter microstructure deteriorates across cognitive stages in Parkinson disease. Neurology 2013;80:1841-1849.
24. Matsui H, Nishinaka K, Oda M, Niikawa H, Kubori T, Udaka F. Dementia in Parkinson's disease: diffusion tensor imaging. Acta Neurol Scand 2007;116:177-181.
25. Acosta-Cabronero J, Williams GB, Pengas G, Nestor PJ. Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. Brain 2010;133:529-539.
26. Duncan GW, Khoo TK, Coleman SY, et al. The incidence of Parkinson's disease in the North-East of England. Age Ageing 2014;43:257-263.
27. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.
28. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-442.
29. Goetz CG, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord 2007;22:41-47.
30. Yesavage JA, Brink TL, Rose TL, et al. Development and Validation of a Geriatric Depression Screening Scale - a Preliminary-Report. Journal of Psychiatric Research 1983;17:37-49.
31. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649-2653.
32. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
33. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
34. Wesnes KA, McKeith IG, Ferrara R, et al. Effects of rivastigmine on cognitive function in dementia with Lewy bodies: A randomised placebo-controlled international study using the Cognitive Drug Research computerised assessment system. Dementia and Geriatric Cognitive Disorders 2002;13:183-192.
35. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia 1994;5:266-281.
36. Benton AL. Differential behavioural effects of frontal lobe disease. Neuropsychologia 1968;6:53-60.
37. Goodglass H. The assessment of aphasia and related disorders. Philadelphia: Lea and Febiger, 1972.
38. Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-Dependent Frontostriatal Planning Deficits in Early Parkinsons-Disease. Neuropsychology 1995;9:126-140.
39. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000;11:805-821.
40. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113.
41. Shen Y, Larkman DJ, Counsell S, Pu IM, Edwards D, Hajnal JV. Correction of high-order eddy current induced geometric distortion in diffusion-weighted echo-planar images. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2004;52:1184-1189.
42. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012;27:349-356.

43. Litvan I, Aarsland D, Adler CH, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord 2011;26:1814-1824.
44. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA neurology 2013;70:580-586.
45. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 2009;44:83-98.
46. Picconi B, Piccoli G, Calabresi P. Synaptic dysfunction in Parkinson's disease. Advances in experimental medicine and biology 2012;970:553-572.
47. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121-134.
48. Pereira JB, Junque C, Marti MJ, Ramirez-Ruiz B, Bartres-Faz D, Tolosa E. Structural brain correlates of verbal fluency in Parkinson's disease. Neuroreport 2009;20:741-744.
49. Henry JD, Crawford JR. Verbal fluency deficits in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc 2004;10:608-622.
50. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007;130:1787-1798.
51. Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry 2013;84:1258-1264.
52. Edden RA, Jones DK. Spatial and orientational heterogeneity in the statistical sensitivity of skeleton-based analyses of diffusion tensor MR imaging data. Journal of neuroscience methods 2011;201:213-219.

Figures

Figure 1. Anatomical location of clusters of reduced gray matter volume associated with cognitive task performance.

Figure 1. Three-dimensional surface renders showing clusters of cortical gray matter loss (red) in those with PD: (a) significant association between poorer performance on the semantic fluency task with gray matter loss in the insular cortex, precentral gyrus, and middle frontal gyrus in the right hemisphere, and the insular cortex and cingulate gyrus in the left hemisphere; (b) in PD impaired on the semantic fluency task relative to controls showing gray matter loss in the right inferior parietal lobule and left transverse temporal gyrus; (c) in PD impaired on the semantic fluency task compared with PD not impaired showing gray matter loss in the right inferior parietal lobule, left insular cortex, and left cingulate gyrus; and (d) association with performance on Tower of London task with areas of reduced gray matter in the right and left insular cortex and the right cingulate gyrus. All results are presented at a cluster-wise threshold corrected $P_{FWE\text{-}corr} < 0.05$.

Figure 2. Associations between MD and performance on the semantic fluency and Tower of London tasks.

Figure 2. Tract-based spatial statistics map showing areas of increased MD (yellow – red) in the white matter in PD overlaid on the study specific mean FA skeleton (green) (A) significant association between increased MD and lower semantic fluency score (B) significant association between increased MD and poorer performance on the executive Tower of London task; and (C) in PD impaired on the semantic fluency task compared with PD not impaired. All results are $P<0.05$, corrected for multiple comparisons using TFCE.

Tables

Table 1. Demographic and clinical characteristics of the Parkinson's disease and control subjects.

Values are mean ± SD, except median (range) for disease duration, education, Hoehn and Yahr stage, GDS, and number (%) for vascular risk factors.

Comparisons between groups performed using [a] Student's *t*-test, [b] Chi-square, [c] Mann-Whitney U test, or [d] Fisher's exact test.

Abbreviations: GDS = Geriatric Depression Scale; MDS-UPDRS-III = Movement Disorders Society revised Unified Parkinson's Disease Rating scale part III

Table 2. Cognitive test data of the Parkinson's disease and control subjects.

Values are median (range) for MMSE, MoCA, Tower of London, spatial recognition memory, pattern recognition memory, and paired associates learning, except for PoA, semantic, and phonemic fluency which are mean ± SD.

Comparisons between groups performed using [a] Mann-Whitney U, [b] Student's *t*-test or [c] Fisher's exact test.

Abbreviations: SD = standard deviation; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment.

Table 3. Anatomical location of clusters of reduced gray matter volume associated with cognitive task performance.

Location and peak significance of significant reduction in gray matter volume: (a) in patients with PD where gray matter volume was associated with performance on the semantic fluency task; (b) in the controls and those PD subjects impaired on the semantic fluency task; (c) in PD subjects with normal performance against those with impaired performance; (d) in PD patients where gray matter volume was associated with performance on the executive Tower of London task. For each peak the table shows cluster-level significance ($p_{FWE\text{-}Corr}$), spatial extent (k), t and z scores, MNI co-ordinates, and anatomical region.

Abbreviations: L = left; MNI = Montreal Neurological Institute; PD = Parkinson's disease; R = right.

GLOSSARY

CANTAB = Cambridge Automated Neuropsychological Test Assessment Battery; CDR = Cognitive Drug Research; CSF = cerebrospinal fluid; DARTEL = diffeomorphic anatomical registration through exponentiated Lie algebra; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders fourth edition; DTI = diffusion tensor imaging; FA = fractional anisotropy; FSL = Functional MRI of the Brain Software Library package; FWE = family-wise error; FWHM = full-width half maximum; GDS-15 = Geriatric Depression Scale; H&Y = Hoehn and Yahr stage; ICICLE-PD = Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in Parkinson's Disease Study; LEDD = levodopa equivalent daily dose; MCI = mild cognitive impairment; MD = mean diffusivity; MDS-UPDRS-III = Movement Disorders Society revised Unified Parkinson's Disease Rating Scale Part III; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; PAL = Paired Associates Learning; PD-MCI = Parkinson's disease with mild cognitive impairment; PoA = Power of Attention; PRM = Pattern Recognition Memory; ROI = region of interest analysis; SF = semantic fluency; SPM = Statistical Parametric Mapping; SRM = Spatial recognition memory; TBSS = tract-based spatial statistics; TE = echo time; TFCE = threshold-free cluster enhancement; TI = inversion time; TIV = total intracranial volume; ToL = Tower of London task; TR = repetition time; VBM = voxel-based morphometry.

Table 1. Demographic and clinical characteristics of the Parkinson's disease and control subjects.

	Control (n = 50)	**PD (n = 125)**	***P* Value**
Demographics			
Age, y	65.8 ± 8.0	66.0 ± 10.5	0.88[a]
Gender, male (% male)	29 (58)	85 (68)	0.21[b]
Education, y	11.5 (3 - 24)	12 (3 – 24)	0.36[c]
Clinical information			
Disease duration, months	-	6.15 (4.66)	-
MDS-UPDRS III	-	26.8 ± 11.1	-
Hoehn and Yahr Stage	-	2 (1 - 3)	-
Levodopa equivalent dose, mg/d	-	175 (0 - 590)	-
GDS-15 (0 - 15)	0 (0 - 7)	2 (0 - 12)	<0.001[c]
Vascular risk factors, n (%)			
Diabetes	1 (2)	10 (8)	0.18[d]
Ischaemic heart disease	3 (6)	13 (10.4)	0.56[d]
Hypertension	13 (26)	38 (30.4)	0.56[b]
Hypercholesterolaemia	10 (20)	16 (12.8)	0.23[b]
Transient ischaemic attack	0 (0)	10 (8)	0.06[d]
Ever smoked	27 (54)	55 (44)	0.26[b]

Values are mean ± SD, except median (range) for disease duration, education, Hoehn and Yahr stage, GDS, and number (%) of vascular risk factors.

Comparisons between groups performed using [a] Student's *t*-test, [b] Chi-square, [c] Mann-Whitney U test, or [d] Fisher's exact test.

Abbreviations: GDS = Geriatric Depression Scale; MDS-UPDRS-III = Movement Disorders Society revised Unified Parkinson's Disease Rating scale part III

Table 2. Cognitive test data of the Parkinson's disease and control subjects.

	Control (n = 50)	**PD (n = 125)**	***P* Value***
Global Cognitive testing			
MMSE (0 - 30)	30 (26 - 30)	29 (24 - 30)	0.003[a]
MoCA (0 – 30)	28 (21 - 30)	26 (16 - 30)	<0.001[a]
Cognitive tests			
Power of attention, ms	1242 ± 116	1363 ± 198	<0.001[b]
Impaired at 1.5 SD, n (%)	2 (4)	28 (22.6)	0.003[c]
Semantic fluency (words)	24.4 ± 6.3	21.2 ± 6.8	0.004[b]
Impaired at 1.5 SD, n (%)	4 (8.0)	19 (15.2)	0.22[c]
Phonemic fluency (words)	41.6 ± 12.9	33.0 ± 12.4	<0.001[b]
Impaired at 1.5 SD, n (%)	3 (6)	20 (16)	0.13[c]
Tower of London (0 – 20)	17 (9 - 20)	15 (1 - 20)	<0.001[a]
Impaired at 1.5 SD, n (%)	3 (6.0)	25 (20.0)	0.07[c]
Spatial recognition memory (0 – 20)	17 (3 - 20)	16 (9 - 20)	<0.001[a]
Impaired at 1.5 SD, n (%)	1 (2)	29 (23.2)	0.004[c]
Pattern recognition memory (0 – 24)	22 (15 - 24)	20 (11 - 24)	0.001[a]
Impaired at 1.5 SD, n (%)	2 (4)	25 (20.0)	0.030[c]
Paired associates learning	1.63 (1.13 -3.57)	1.88 (1 - 7)	0.002[b]

Impaired at 1.5 SD, n (%)	3 (6)	17 (13.6)	0.35[c]

Values are median (range) for MMSE, MoCA, Tower of London, spatial recognition memory, pattern recognition memory, and paired associates learning, except for PoA, semantic, and phonemic fluency which are mean ± SD.

Comparisons between groups performed using [a] Mann-Whitney U, [b] Student's *t*-test or [c] Fisher's exact test.

* Following Bonferroni correction for multiple neuropsychological tests, $p < 0.007$ was considered a significant difference in test scores between subjects with PD and controls.

Abbreviations: SD = standard deviation; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment.

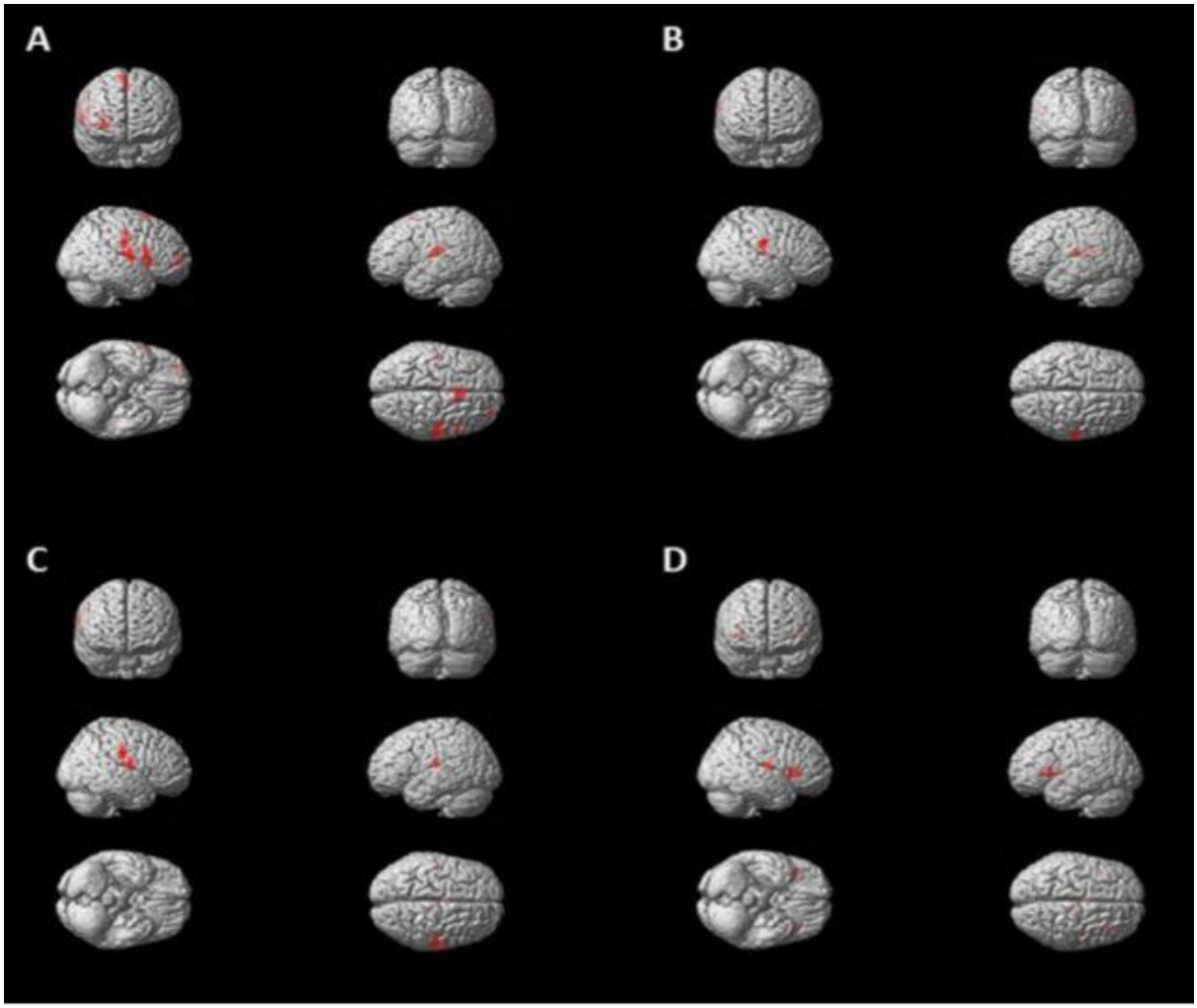
Table 3. Anatomical location of clusters of reduced gray matter volume associated with cognitive task performance.

Brain Region	**Cluster-Wise value** ($p_{FWE\text{-}corr}$)	**Cluster size (k)**	**Peak voxel T, Z**	**MNI Co-ordinates (mm)**		
				X	**Y**	**Z**
(a) Association between gray matter volume and semantic fluency scores						
R insular cortex	0.001	3092	5.73, 5.37	45	-12	10
R precentral gyrus	0.002	1697	5.26, 4.97	59	12	10
R middle frontal gyrus	0.037	871	4.60, 4.40	30	59	1
L insular cortex	0.003	1605	5.07, 4.81	-48	-18	16
L cingulate gyrus	0.002	1792	4.23, 4.07	-3	-9	45
(b) Controls > $PD_{\text{-impaired-semantic fluency}}$						
R inferior parietal lobule	0.040	888	4.66, 4.31	63	-19	27
L transverse temporal gyrus	0.013	1217	4.47, 4.16	-51	-21	12
(c) PD-NC > $PD_{\text{-impaired-semantic fluency}}$						
R inferior parietal lobule	0.001	2189	4.57	64	-19	27
L insular cortex	0.028	1006	4.17, 4.01	-42	-18	12
L cingulate gyrus	0.035	947	4.13, 3.98	-4	-10	45
(d) Association between gray matter volume and performance on Tower of London task						

R insular cortex	0.002	1848	5.61, 5.26	41	21	-0
R insular cortex	0.020	1070	4.55, 4.35	39	-12	15
R cingulate gyrus	0.031	956	4.38, 4.20	9	-30	45
L insular cortex	0.005	1524	5.08, 4.81	-39	17	3

Location and peak significance of significant reduction in gray matter volume: (a) in patients with PD where gray matter volume was associated with performance on the semantic fluency task; (b) in the controls and those PD subjects impaired on the semantic fluency task; (c) in PD subjects with normal performance against those with impaired performance; (d) in PD patients where gray matter volume was associated with performance on the executive Tower of London task. For each peak the table shows cluster-level significance ($p_{FWE\text{-}Corr}$), spatial extent (k), t and z scores, MNI co-ordinates, and anatomical region.

Abbreviations: L = left; MNI = Montreal Neurological Institute; PD = Parkinson's disease; R = right.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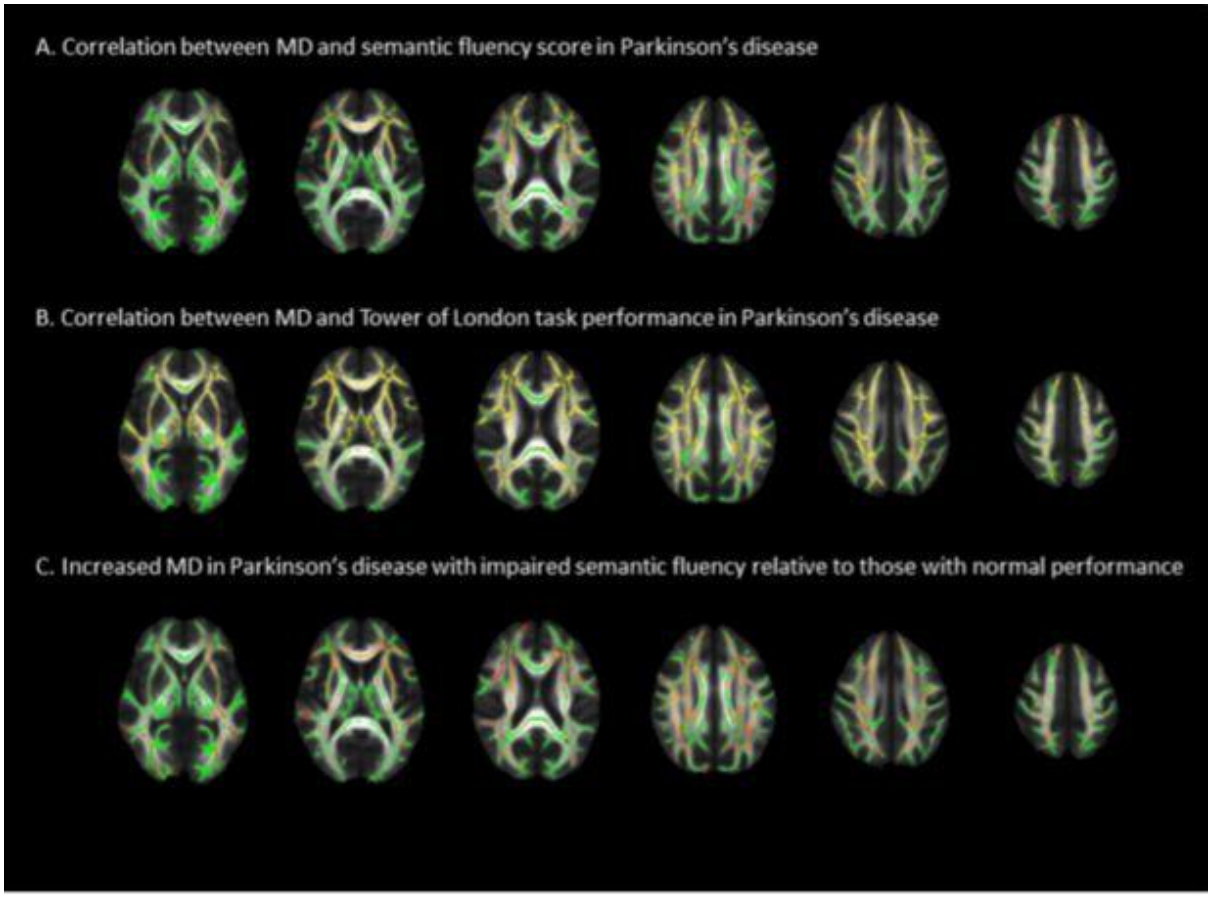
A. Correlation between MD and semantic fluency score in Parkinson's disease
B. Correlation between MD and Tower of London task performance in Parkinson's disease
C. Increased MD in Parkinson's disease with impaired semantic fluency relative to those with normal performance